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(54) Title: NOVEL FORMULATION CONTAINING PAROXETINE

(57) Abstract

Paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into capsules under conditions such there is no detectable conversion to hemihydrate during the manufacturing process.

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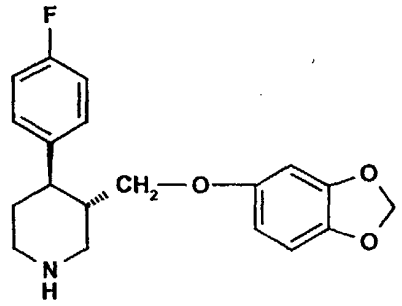
NOVEL FORMULATION CONTAINING PAROXETINE

The present invention relates to novel formulations and to the use of the formulations in the treatment and/or prevention of certain disorders.

US Patent 4,007,196 describes certain compounds which possess anti-depressant activity. One specific compound mentioned in this patent is known as paroxetine and has the following formula:



This compound has been approved for human use and is marketed, in the form of its hydrochloride salt, in many countries around the world as an anti-depressant agent.

All paroxetine hydrochloride sold to date has been in the form of oral swallow tablets, containing the hemihydrate, which is described in EP-0 223 403. Paroxetine hydrochloride has been reported as also existing as an anhydrate. WO 96/24595 describes the preparation and physical properties of four different polymorphic forms (Forms A, B, C and D) of the anhydrate.

WO 95/16448 discloses that paroxetine is likely to develop a pink colour unless it is formulated into tablets using a formulation process in which water is absent, such as dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets. The term "dry" was used to denote substantially dry as opposed to the wholesale addition of water which had been previously employed in the wet granulation process.

It has now surprisingly been found that, even under these relatively dry conditions, paroxetine hydrochloride anhydrate has a tendency to convert at least partially to the hemihydrate during the tabletting process. Although not dangerous, this creates difficulties in establishing and maintaining a reference standard for regulatory and quality control purposes.

Accordingly, the present invention provides paroxetine hydrochloride in a form other than the hemihydrate, which is formulated into capsules under conditions such there is no detectable conversion to hemihydrate during the manufacturing process.

The paroxetine hydrochloride may, for example, be present in an amorphous form or as a crystalline anhydrate.

This can be achieved for example by the use of either excipients which are essentially anhydrous for powder fill capsules (that is to say, they contain less than 2%, more especially less than 1.5%, preferably less than 1% water) or excipients which are essentially hydrophobic for solid or liquid filled capsules.

It has been found for example that dibasic calcium phosphate anhydrous and polyglycolized glycerides can be used to form oral swallow capsules with paroxetine hydrochloride anhydrate without undesired conversion to hemihydrate during the manufacturing process. The capsules are then packaged with a desiccant in order to prevent conversion of anhydrate to hemihydrate on storage.

Accordingly, the present invention also provides a process for the preparation of paroxetine hydrochloride anhydrate capsules free of detectable hemihydrate which is characterised by the use of conditions such there is no detectable conversion of the anhydrate to hemihydrate during the manufacturing process. Such conditions can be achieved by the use of essentially anhydrous/hydrophobic excipients under conditions of low relative humidity

Examples of excipients with the necessary low moisture content include materials such as dibasic calcium phosphate anhydrous, anhydrous direct compression lactose, monosaccharide sugars eg mannitol, disaccharide sugars eg lactitol, powdered cellulose, pregelatinised starch and similar materials. These materials may also be of a grade suitable for direct compression, as this can aid powder filling on the capsule filling machine and also impart appropriate compression characteristics on the blend as appropriate for certain types of capsule filling machines. Dibasic calcium phosphate anhydrous is commercially available in a pharmaceutically acceptable grade, eg A-TAB (Rhone Poulenc) as the main excipient in a powder fill capsules formulation. In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with dibasic calcium phosphate anhydrous and other pharmaceutically acceptable excipients such as a lubricant eg magnesium stearate and mixed in a suitable blender before filling cellulose capsule shells of intrinsically low moisture content (eg Shionogi Qualicaps, < 3%). Additionally, certain of the low

moisture sugars are available in direct compression grades eg mannitol and lactitol; direct compression lactilol is commercially available in a pharmaceutically acceptable grade, eg Finlac DC (Xyrofin). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with direct compression lactilol and other pharmaceutically acceptable excipients such as a lubricant eg magnesium stearate and mixed in a suitable blender before filling cellulose capsule shells of intrinsically low moisture content (eg Shionogi Qualicaps, < 3%).

Examples of excipients with the necessary hydrophobicity include materials such as polyglycolised glycerides eg Gelucire 44/14; complex fatty materials of plant origin eg theobroma oil, carnauba wax; plant oils eg peanut, olive, palm kernels, cotton, corn, soya; hydrogenated plant oils eg peanut, palm kernels, cotton, soya, castor, coconut; natural fatty materials of animal origin eg beeswax, lanolin, fatty alcohols eg cetyl, stearyl, lauric, myristic, palmitic, stearic; esters eg glycerol stearate, glycol stearate, ethyl oleate, isopropyl myristate; solid interesterified semi-synthetic glycerides eg suppocire, witepsol; liquid interesterified semi-synthetic glycerides eg miglyol 810/812, labrafil; amide or fatty acid alcolamides eg stearamide ethanol, diethanolamide of fatty coconut acids; polyoxyethylene glycols eg PEG 400, PEG 600, PEG 4000.

An appropriate plant oil eg peanut oil (arachis oil) is commercially available in a pharmaceutically acceptable grade eg Lipex 101 (Karlshamns). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with warm Lipex 101 in a suitable blender (to form a suspension) before filling into gelatin capsule shells.

A hydrogenated plant oil is commercially available in a pharmaceutically acceptable grade eg Lubritab (Edward Mendell). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with molten Lubritab in a suitable blender, a hydrophilic excipent, for example anhydrous lactose is added (to form a suspension) before filling into gelatin capsule shells.

An appropriate fatty alcohol eg cetyl alcohol is commercially available in a pharmaceutically acceptable grade eg Crodacol C95 (Croda). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with molten Crodacol C95 in a suitable blender (to form a suspension) before filling into gelatin capsule shells.

A polyglycolised glyceride is commercially available in a pharmaceutically acceptable grade eg Gelucire 44/14 (Gattfosse). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with molten Gelucire 44/14 in a suitable blender (to form a solid suspension) before filling gelatin capsule shells.

A liquid interesterified semi-synthetic glycerides is commercially available in a pharmaceutically acceptable grade eg Labrafil M 2125CS (Gattfosse) or Miglyol 810/812 (Hull). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with Labrafil M 2125CS (Gatfosse) to produce a suspension in a hard or soft gelatin capsule formulation. Alternatively, paroxetine hydrochloride anhydrate is mixed with Miglyol 810 (H©ls AG) in a suitable mixer to produce a suspension in a hard or soft gelatin capsule formulation.

A solid interesterified semi-synthetic glycerides is commercially available in a pharmaceutically acceptable grade eg Suppocire AM - DM (Gattfosse). In a particular process of the invention, (example 4) paroxetine hydrochloride anhydrate is mixed with molten Suppocire DM in a suitable blender (to form a suspension) before filling into gelatin capsule shells.

The capsule formulation is packaged in standard pharmaceutical container/closure presentations, optionally with a desiccant.

The amount of paroxetine used is adjusted such that in a single unit dose there is a therapeutically effective amount of paroxetine. Preferably the unit dose contains from 10 to 100 mg paroxetine (as measured in terms of the free base). More preferable the amount of paroxetine in a unit dose is 10mg, 20mg, 30mg, 40mg or 50mg. The most preferred amount of paroxetine in a unit dose is 20mg.
Paroxetine used in the formulation is in the form of the hydrochloride anhydrate which may be prepared according to the procedures outlined in WO 96/24595. Suitable procedures for preparing paroxetine include those mentioned in US Patents 4,009,196, 4,902,801, 4,861,893 and 5,039,803 and PCT/GB 93/00721.

It has been mentioned that paroxetine has particular utility in the treatment of depression; paroxetine may also be used in the treatment of mixed anxiety and depression, obsessive compulsive disorders, panic, pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia and the depression arising from pre-menstrual tension and adolescence.

The present invention therefore also provides a method of treating or preventing any of the above disorders which comprises administering an effective or prophylactic amount of an oral swallow capsule prepared in accordance with the present invention.

The following examples illustrate the present invention:

Example 1

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	225.28
Magnesium Stearate	2.50
Capsule weight	250.00

Example 2

	mg
Paroxetine hydrochloride †	22.22
Direct compression Lactitol	225.28
Magnesium Stearate	2.50
Capsule weight	250.00

Example 3

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	225.28
Magnesium Stearate	2.50
Capsule weight	250.00

Example 4

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	175.78
Magnesium Stearate	2.00
Capsule weight	200.00

Example 5

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	126.28
Magnesium Stearate	1.50
Capsule weight	150.00

Example 6

	mg
Paroxetine hydrochloride †	22.22
Lipex 101	227.78
Capsule weight	250.00

Example 7

	mg
Paroxetine hydrochloride †	22.22
Anhydrous Lactose	50.0
Lubritab	177.78
Capsule weight	250.00

Example 8

	mg
Paroxetine hydrochloride †	22.22
Crodacol C95	227.78
Capsule weight	250.00

Example 9

	mg
Paroxetine hydrochloride †	22.22
Gelucire 44/14	227.78
Capsule weight	250.00

Example 10

	mg
Paroxetine hydrochloride †	22.22
Labrafil M 2125CS	227.78
Capsule weight	250.00

Example 11

	mg
Paroxetine hydrochloride †	22.22
Miglyol 810	227.78
Capsule weight	250.00

Example 12

	mg
Paroxetine hydrochloride †	22.22
Suppocire DM	227.78
Capsule weight	250.00

† Equivalent to 20 mg of Paroxetine on an anhydrous free base basis

Claims

1. Paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into capsules under conditions such there is no detectable conversion to hemihydrate during the manufacturing process.

2. Paroxetine hydrochloride according to claim 1 which is amorphous or in the form of a crystalline anhydrate.

3. A process for the preparation of paroxetine hydrochloride capsules free of detectable hemihydrate which is characterised by the use of conditions such there is no detectable conversion to hemihydrate during the tabletting process.

4. A process according to claim 3 which is carried out using essentially anhydrous and/or hydrophobic excipients.

5. A process according to claim 4 wherein the excipients are chosen from the group consisting of dibasic calcium phosphate anhydrous, anhydrous direct compression lactose, monosaccharide sugars, disaccharide sugars, powdered cellulose, and pregelatinised starch.

6. A process according to claim 4 wherein the excipients are chosen from the group consisting of polyglycolised glycerides; complex fatty materials of plant origin, plant oils, hydrogenated plant oils, natural fatty materials of animal origin, fatty alcohols; esters; solid interesterified semi-synthetic glycerides; liquid interesterified semi-synthetic glycerides; amide or fatty acid alcolamides; and polyoxyethylene glycols.

7. A process according to any one of claims 3 to 6 which is carried out under conditions of low relative humidity.

8. A kit of parts comprising capsules according to claim 1or 2 or obtainable by the process of any one of claims 3 to 7, together with a desiccant.